

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**

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Sheet 1 of 1

Complete if Known

Application Number	10/681,418
Filing Date	October 7, 2003
First Named Inventor	H. Michael SHEPARD
Art Unit	1623
Examiner Name	Crane, Lawrence E.
Attorney Docket Number	NB 2008.01; 060925-0801

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No. ¹	Document Number Number - Kind Code ² (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Application of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
<i>me</i>	C 1	US-6,589,941 B1	07-08-2003	Fahrtg et al.	
	C 2	US-6,599,499	07-29-2003	Rosen et al.	
	C 3	US-6,677,314	01-13-2004	Klecker et al.	
	C 4	US-6,677,315	01-13-2004	Klecker et al.	
	C 5	US-6,682,715	01-27-2004	Klecker et al.	
	C 6	US-6,683,045	01-27-2004	Klecker et al.	
<i>me</i>	C 7	US-6,703,374	03-09-2004	Klecker et al.	
	8	US-			
	9	US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. ¹	Foreign Patent Document Country Code ³ - Number ⁴ - Kind Code ⁵ (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Application of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ⁶
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Examiner's
Signature

L. E. Crane

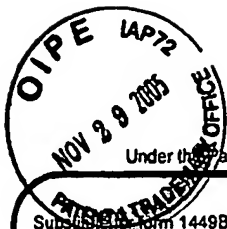
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Sheet	1	of	2		

NON PATENT LITERATURE DOCUMENTS				
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher city and/or country where published	T ²	
	CC 1	BATHE et al. "Increased thymidylate synthase gene expression in liver metastases from colorectal carcinoma: implications for chemotherapeutic options and survival" <i>Cancer J. Sci. Am.</i> (1999) 5(1):34-40		
	CC 2	BELT et al. "Nucleoside Transport in Normal and Neoplastic Cells" <i>Advan. Enzyme Regul.</i> (1993) 33:235-252		
	CC 3	BIBLE et al. "Cytotoxic synergy between flavopiridol (NSC 649890, L86-8275) and various antineoplastic agents: the importance of sequence of administration" <i>Cancer Res.</i> (August 15, 1997) 57(16):3375-80		
	CC 4	CHOU and TALALAY, "Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors" <i>Adv. Enzyme Regul.</i> (1984) 22:27-55		
	CC 5	CURT "Cancer drug development: new targets for cancer treatment" <i>Oncologist</i> (1996) 1(3):II-III		
	CC 6	CURTIN et al. "Mechanism of Cell Death following Thymidylate Synthase Inhibition: 2'-Deoxyuridine-5'-triphosphate Accumulation, DNA Damage, and Growth Inhibition following Exposure to CB3717 and Dipyridamole" <i>Cancer Res.</i> (May 1, 1991) 51:2346-2352		
	CC 7	GOEL et al. "Selective Intraperitoneal Biochemical Modulation of Methotrexate by Dipyridamole" <i>J. Clin. Oncol.</i> (February 1989) 7(2):262-269		
	CC 8	GORLICK et al. "Drug Resistance in Colon Cancer" <i>Semin. Oncol.</i> (December 1999) 26(6):606-611		
	CC 9	GREM "Biochemical modulation of fluorouracil by dipyridamole: preclinical and clinical experience" <i>Semin Oncol.</i> (April 1992) 19(2 Suppl 3):56-65		
	CC 10	GRIFFITH et al. "Differential Inhibition of Nucleoside Transport Systems in Mammalian Cells by a New Series of Compounds Related to Lidoflazine and Mioflazine" <i>Biochem. Pharmacol.</i> (1990) 40(10):2297-2303		
	CC 11	KRAUPP et al. "Membrane Transport of Nucleobases: Interaction with Inhibitors" <i>Gen. Pharmacol.</i> (1995) 26(6):1185-1190		
	CC 12	LACKEY et al. "Enzyme-catalyzed therapeutic agent (ECTA) design: activation of the antitumor ECTA compound NB1011 by thymidylate synthase" <i>Biochem. Pharmacol.</i> (2001) 61:179-189		
	CC 13	LEHMAN et al. "Modulation of RTX cytotoxicity by thymidine and dipyridamole in vitro: implications for chemotherapy" <i>Cancer Chemother. Pharmacol.</i> (2000) 45:142-148		
	CC 14	LEICHMAN et al. "Quantitation of Intratumoral Thymidylate Synthase Expression Predicts for Disseminated Colorectal Cancer Response and Resistance to Protracted-Infusion Fluorouracil and Weekly Leucovorin" <i>J. Clin. Oncol.</i> (October 1997) 15(10):3223-3229		
	CC 15	LEICHMAN "Thymidylate synthase as a predictor of response" <i>Oncol.</i> (August 1998) 12(8Suppl.6):43-47		
	CC 16	LENZ et al. "Rapid quantitative PCR for determination of relative gene expressions in tissue specimens" <i>PCR Methods Appl.</i> (1995) 4:305-308		
Examiner's Signature	L. E. Crane		Date Considered	01/09/2006

* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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NON PATENT LITERATURE DOCUMENTS

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Signature**

L. E. Crane

Date
Considered

01/09/2006

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Form PTO-892 U.S. Department of Commerce	Serial Number 10/681,418	Group Art Unit 1623	Attachment to Paper Number 01122006	
Notice of References Cited	APPLICANT(S) Shepard et al.			


Published U. S. Patent Applications†††

*		DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS	Filing Date If Appropriate
*	P 1	2001/0034440 A1	10/25/01	Shepard et al. (I)	536	026.800	
*	P 2	2002/0147175 A1	10/10/02	Shepard et al. (II)	514	049.000	
*	P 3	2002/0151519 A1	10/17/02	Shepard et al. (III)	514	050.000	

U. S. Patent Documents†††

*		DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS	Filing Date If Appropriate
*	A	5,212,291 A	05/18/93	Murdock et al. (I)	536	006.400	
*	B	5,116,827 A	05/26/92	Murdock et al. (II)	514	082.000	
*	C	5,070,082 A	12/03/91	Murdock et al. (III)	514	105.000	
*	D	5,077,283 A	12/31/91	Murdock et al. (IV)	514	094.000	
*	E	5,077,282 A	12/31/91	Murdock et al. (V)	514	080.000	
*	F	5,616,564 A	04/01/97	Rapaport et al.	514	044.000	01/07/94
*	G	6,245,750 B1	06/12/01	Shepard (I)	514	051.000	
*	H	5,457,187 A	10/10/95	Gmeiner et al.	536	025.500	
*	I	5,212,161 A	05/18/93	Moriniere et al.	514	050.000	
*	J	3,852,266 A	12/03/74	Kiyanagi et al.	536	028.550	
*	K	6,339,151 B1	02/15/02	Shepard et al. (IV)	536	026.800	
*	AA	6,495,553 B1	12/17/02	Shepard (II)	514	256.000	
*	AB	6,683,061 B1	01/27/04	Shepard et al. (V)	514	050.000	

††† References cited by examiner in related cases 10/119,927 and 09/782,721.

EXAMINER L. E. Crane 	DATE 01/09/06	page 1 of 6 ¥: Reference not presently available.
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Form PTO-892 U.S. Department of Commerce	Serial Number 10/681,418	Group Art Unit 1623	Attachment to Paper Number 01122006	
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Foreign Patent Documents†††

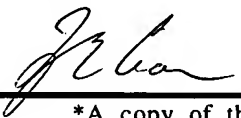
*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS		
*	L	WO 95/08556 A1	03/30/95	World(WO/PCT)	Amersham Intl.	-----	-----		
*	M	WO 99/20741 A1	04/29/99	World(WO/PCT)	Geron Corp.	-----	-----		
*	N	WO 96/40708 A1	12/19/96	World(WO/PCT)	La Jolla Pharm. Co	-----	-----		
*	O	WO 96/10300 A1	04/04/96	World(WO/PCT)	Isis Pharm., Inc.	-----	-----		
*	P	WO 94/22483 A2	10/13/94	World(WO/PCT)	D-Pharm Ltd.	-----	-----		
*	Q	WO 96/03151 A2	02/08/96	World(WO/PCT)	Cancer Res.	-----	-----		
*	AL	WO 96/07431 A1	03/14/96	World(WO/PCT)	U. GA. Res. Fndtn.	-----	-----		
*	AM	WO 97/28179 A1	08/07/97	World(WO/PCT)	Regnts U. Calif.	-----	-----		
*	AN	GB 982,776	02/10/65	G. Britain	Wellcome Fndtn	-----	-----		
*	AO	WO 01/07454 A1	02/01/01	World(WO/PCT)	Newbiotics, Inc.(I)	-----	-----		
*	AP	WO 99/08110 A1	02/18/99	World(WO/PCT)	Newbiotics, Inc. (II)	-----	-----		
*	AQ	WO 99/37753 A1	07/29/99	World(WO/PCT)	Newbiotics, Inc. (III)	-----	-----		

Other References†††(Including Author, Title, Date, Pertinent Pages, etc.)

*	R	Firestone et al., "A Comparison of the Effects of Antitumor Agents Upon Normal Human Epidermal Keratinocytes and Human Squamous Cell Carcinoma," <i>Journal of Investigative Dermatology</i> , 94(5), 657-661 (May, 1990).
*	S	Dagle et al., "Targeted Degradation of mRNA in <i>Xenopus</i> oocytes and Embryos Directed by Modified Oligonucleotides: Studies of An2 and Cyclin in Embryogenesis," <i>Nucleic Acids Research</i> , 18(16), 4751-4757 (August 25, 1990).

† Month of publication data is unavailable. Issue Number information is provided whenever possible following the volume number in parentheses.

††† References cited by examiner in related cases 10/119,927 and 09/782,721.


EXAMINER L. E. Crane 	DATE 01/09/06	page 2 of 6 ¥: Reference not presently available.
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	Shepard et al.			

Other References (Including Author, Title, Date, Pertinent Pages, etc.)

* T	Hakimelahi et al., "Design, Synthesis, and Structure-Activity Relationship of Novel Dinucleotide Analogs as Agents Against Herpes and Human Immunodeficiency Viruses," <i>Journal of Medicinal Chemistry</i> , 38(23), 4648-4659 (November 10, 1995).
* U	Naesens et al., "Anti-HIV Activity and Metabolism of Phosphoramidate Derivatives of D4T-MP with Variations in the Amino Acid Moiety," Poster Session 1, <u>The Tenth International Conference on Antiviral Research</u> , Hotel Nikko, Atlanta, GA, April 6-11, 1997; published in <i>Antiviral Research</i> , 34(2), p. A54 (Abstract 40), (April, 1997).
* V†	Evrard et al., "An <i>in vitro</i> Nucleoside Analog Screening Method for Cancer Gene Therapy," <i>Cell Biology and Toxicology</i> , 12, 345-350 (1996).
* W†	Berkow et al. (eds.), <u>The Merck Manual of Diagnosis and Therapy</u> , 16th Ed., Merck & Co., Rahway, NJ, May, 1992, only page 1278 supplied.
* X†	Morrison & Boyd (eds.), <u>Organic Chemistry</u> , Allyn & Bacon, Inc., Boston, MA, 1973, only pages 1170-1180 supplied.
* Y†	L. B. Townsend (ed.), <u>Chemistry of Nucleosides and Nucleotides</u> , Volume 3, Plenum Press, New York, NY, 1974, only Table of Contents, Bibliography pages 529-535, and Index pages 537-552 supplied.
* Z†	<u>The American Heritage College Dictionary</u> , Third Edition, Houghton Mifflin Co., New York, NY, 1997, only page 668 supplied.
* RA†	Barr et al., "Inhibition of Thymidylate Synthetase by 5-Alkynyl-2'-deoxyuridylates," <i>Journal of Medicinal Chemistry</i> , 24(12), 1385-1388 (1981).

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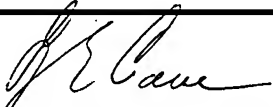
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Other References (Including Author, Title, Date, Pertinent Pages, etc.)

*	SA†	Bergstrom et al. , "Synthesis of (<i>E</i>)-5-(3,3,3-Trifluoro-1-propenyl)-2'-deoxyuridine and Related Analogues: Potent and Unusually Selective Antiviral Activity of (<i>E</i>)-5-(3,3,3-Trifluoro-1-propenyl)-2'-deoxyuridine Against Herpes Simplex Virus Type 1," <i>Journal of Medicinal Chemistry</i> , 27(3), 279-284 (1984).
*	TA	Bigge et al. , "Palladium-Catalyzed Coupling Reactions of Uracil Nucleosides and Nucleotides," <i>J. American Chemical Society</i> , 102(6), 2033-2038 (March 12, 1980).
*	UA†	Cho et al. , "(<i>E</i>)-5-(3-Oxopropen-1-yl)-2'-deoxyuridine and (<i>E</i>)-5-(Oxopropen-1-yl)-2',3'-dideoxyuridine; New Antiviral Agents: Syntheses and Biological Activity," <i>Tetrahedron Letters</i> , 35(8), 1149-1152 (1994).
*	VA†	Crisp, G. T. , "Synthesis of 5-Alkenyl-2'-deoxyuridines via Organostannanes," <i>Synthetic Communications</i> , 19(11&12), 2117-2123 (1989).
*	WA†	Fries et al. , "Synthesis and Biological Evaluation of 5-Fluoro-2'-deoxyuridine Phosphoramidate Analogs," <i>Journal of Medicinal Chemistry</i> , 38(14), 2672-2680 (1995).
*	YA†	Hobbs, F. W., Jr. , "Palladium Catalyzed Synthesis of Alkynylamino Nucleosides. A Universal Linker for Nucleic Acids," <i>Journal of Organic Chemistry</i> , 54(14), 3420-3422 (1989).
*	ZA†	Hsiao et al. , "Synthesis of 5'-ThymidinyI Bis(1-aziridinyl)phosphonates as Antineoplastic Agents," <i>Journal of Medicinal Chemistry</i> , 24(7), 887-889 (1981).

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Other References (Including Author, Title, Date, Pertinent Pages, etc.)

*	RB†	Krajewska et al. , "Pyrimidine Ribonucleoside Phosphorylase Activity vs 5- and/or 6-Substituted Uracil and Uridine Analogues, Including Conformational Aspects," <i>Biochemical Pharmacology</i> , 31(6), 1097-1102 (1982).
*	SB	McIntee et al. , "Probing the Mechanism of Action and Decomposition of Amino Acid Phosphoramidates of Antiviral Nucleoside Prodrugs," <i>Journal of Medicinal Chemistry</i> , 40(21), 3323-3331 (1997); published in <i>Advance ACS Abstracts</i> , September 15, 1997).
*	TB†	Robins et al. (I) , "Nucleic Acid Related Compounds. 31. Smooth and Efficient Palladium-Copper Catalyzed Coupling of Terminal Alkynes with 5-Iodouracil Nucleosides," <i>Tetrahedron Letters</i> , 22, 421-424 (1981).
*	UB†	Robins et al. (II) , "Nucleic Acid Related Compounds. 39. Efficient Conversion of 5-Iodo to 5-Alkynyl and Derived 5-Substituted Uracil Bases and Nucleosides," <i>Journal of Organic Chemistry</i> , 48(11), 1854-1862 (1983).
*	VB†	Ruth et al. , "C-5 Substituted Pyrimidine Nucleosides. 1. Synthesis of C-5 Allyl, Propyl, and Propenyl Uracil and Cytosine Nucleosides via Organopalladium Intermediates," <i>Journal of Organic Chemistry</i> , 43(14), 2870-2876 (1978).
*	WB†	Griengl et al. , "Phosphonoformate and Phosphonoacetate Derivatives of 5-Substituted 2'-Deoxyuridines: Synthesis and Antiviral Activity," <i>Journal of Medicinal Chemistry</i> , 31(9), 1831-1839 (1988).

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* XB	Gonen et al., "Thymidylate Synthase Expression in Hepatic Tumors Is a Predictor of Survival and Progression in Patients With Resectable Hetastatic Colorectal Cancer," <i>Journal of Clinical Oncology</i> , 21(3), 406-412 (February 1, 2003).††
* YB	Rahman et al., "Elevated Levels of Thymidylate Synthase Linked to Cancer Etiology," <i>Cancer Cell</i> , 5, 341-351 (2004); summarized in <i>CCR/Frontiers in Science</i> , 4, 6-7 (March, 2005).††

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